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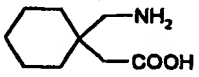
(54) Title: PROCESS FOR THE SYNTHESIS OF 1–(AMINOMETHYL)CYCLOHEXYL–ACETIC ACID



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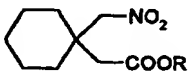

(II)

(57) Abstract

The invention relates to a new process for the synthesis of 1–(aminomethyl)cyclohexyl–acetic acid of formula (I) via the new intermedier 1–(nitromethyl)cyclohexyl–acetic acid derivative of formula (II), wherein R represents hydrogen, benzyl group, diphenylmethyl group or C_1–C_4 alkyl or alkoxy aromatic ring substituted derivatives thereof.

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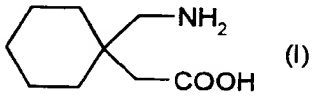
Process for the synthesis of 1-(aminomethyl)cyclohexyl-acetic acid

The invention relates to a new process for the synthesis of 1-(aminomethyl)cyclohexyl-acetic acid of the formula (I) via the new intermedier 1-(nitromethyl)cyclohexyl-acetic acid derivative of general formula (II), wherein R represents hydrogen, benzyl group, diphenylmethyl group or C_1-C_4 alkyl or alkoxy aromatic ring substituted derivatives thereof.



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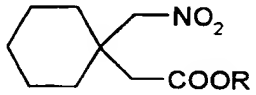


(II)

The 1-(aminomethyl)cyclohexyl-acetic acid of formula (I), otherwise known as gabapentin is the active ingredient of the GABA antagonist drug. Several methods are known from the literature for the synthesis of this compound.

In most of the known methods an intermedier is hydrolysed with acid, and gabapentin is obtained from the so formed gabapentin hydrochloride salt by using ion exchange resin. This process is described in the German patent No. DE 2 460 891, in which the 1,1-cyclohexyldiacetic acid anhydride is converted into hydroxamic acid and the latter is transformed via Lossen degradation into the hydrochloride salt of the product. The US patent No. US 4 024 175 describes a method where the same 1,1-cyclohexyldiacetic acid anhydride is used as starting material. The anhydride is first transformed into a monomethyl ester monosalt and then a monoacid monoazide is obtained from it. The gabapentin hydrochloride is prepared from the latter via Curtius degradation.

Similarly gabapentin hydrochloride is formed in the procedure described in the European patent No. EP 414 274. According to this

invention the alkyl ester of 1-(nitromethyl)acetic acid is transformed into a 2-aza-spiro[4,5]decane-3-on derivative by catalytic hydrogenation. The gabapentin hydrochloride is obtained from the latter lactam derivative by refluxing it with hydrochloric acid and gabapentin is isolated by using ion-exchange resin.

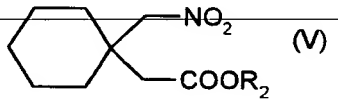
The disadvantages of the above mentioned procedures are as follows. The gabapentin is obtained as its hydrochloride salt and gabapentin itself can be isolated only by using labour-demanding and expensive ion-exchange method. To avoid the unwanted lactam formation side-reaction requires also a labour-demanding and expensive technique. Further disadvantages of these procedures are the use of hazardous reagents, e.g. potassium cyanide, sodium azide and the expensive pressure resistant equipment.

The procedure described in the European patent No. EP 414 275 avoids the formation of the lactam compound and the gabapentin hydrochloride, and this way the use of the expensive ion-exchange method. According to this procedure cyano-cyclohexane-maleinic acid derivatives are hydrolysed with base, decarboxylated and finally the nitril group is catalytically hydrogenated. On the other hand this patent does not describe the synthesis of the cyano-cyclohexane-maleinic acid derivatives, which is a multi step, tedious process. It is important to note, that the synthesis of the maleinic acid ester is four steps starting from cyclohexanon, so the synthesis of gabapentin is altogether seven steps. The patent does not mention the purity of the obtained gabapentin either, in contrast to other patents, which describe the synthesis of gabapentin, e.g. EP 414 274.

The aim the invention is to elaborate an economical, industrially applicable process for the synthesis of gabapentin, which eliminates the disadvantages of the above mentioned procedures and makes possible the simple synthesis of the very pure final product of formula (I) in fewer steps and in good yield.

The synthesis of gabapentin according to the process of the invention is as follows

a) the alkyl ester of cyclohexylidene-acetic acid of general formula (VI) — wherein R_2 represents C_1-C_4 alkyl group — is transformed into the alkyl ester of 1-(nitromethyl)cyclohexyl-acetic acid of general formula (V) — wherein the meaning of R_2 is as defined above — with nitromethane in the presence of a base, the latter is hydrolysed with aqueous methanolic solution of potassium hydroxide and the obtained 1-(nitromethyl)cyclohexyl-acetic acid of formula (IIa) is hydrogenated in a solvent in the presence of a catalyst to yield the desired product of formula (I), or



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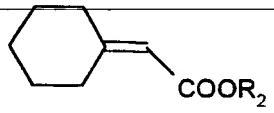

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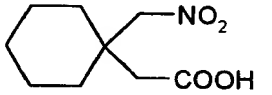
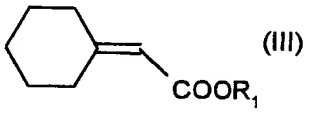


(IIa)

b) the alkyl ester of cyclohexylidene-acetic acid of general formula (VI) — wherein the meaning of R_2 is as defined above — is hydrolysed with aqueous methanolic solution of potassium hydroxide and the obtained cyclohexylidene-acetic acid of formula (IV) is reacted with a reagent of formula R_1-X — wherein R_1 represents benzyl group, diphenylmethyl group or in given case C_1-C_4 alkyl or alkoxy aromatic ring substituted derivatives thereof — to give the appropriate cyclohexylidene acid derivative of general formula (III) — wherein the meaning of R_1 is as defined above — and this intermedier is transformed into 1-(nitromethyl)cyclohexyl-acetic acid derivative of general formula (IIb) —

wherein the meaning of R_1 is as defined above — with nitromethane and the latter is hydrogenated in a solvent in the presence of a catalyst.



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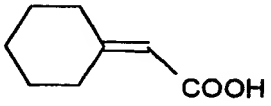

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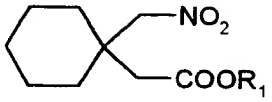


(IIb)

The process of the invention is illustrated on Scheme 1.

The invention based on the observation, that the reduction of the new compounds of general formula (II) at atmospheric pressure yields directly the pure desired final product.

Surprisingly it was found, that using the compounds of general formula (II) as starting materials in the reduction step the lactam compound is not formed, but the very pure gabapentin is obtained directly. This was not anticipated in the knowledge of previous procedures, as the ability of lactam formation of this type of compounds is known from the literature (e.g. EP 414 274).

The alkyl ester of cyclohexylideneacetic acid of general formula (VI) used as starting material can be prepared according to the literature via the reaction of cyclohexanone and the appropriate ester of diethylphosphono-acetic acid.

In the last hydrogenation step any catalysts can be used, which are generally applicable in hydrogenation reactions, rare metal catalysts, e.g. rhodium or palladium, Raney nickel or cobalt catalysts, in given case on a carrier e.g. on carbon, preferably palladium on activated carbon, more preferably 10% of the compound to be reduced.

The hydrogenation is carried out in an inert organic solvent, preferably in a C_1-C_4 alcohol, more preferably in methanol, at 10-50°C,

under 1-20 kPa pressure, preferably at room temperature and under atmospheric pressure.

The Michael addition of the ester of cyclohexylidene-acetic acid with nitromethane is carried out in the presence of a base, preferably potassium hydroxide.

The hydrolysis of the alkyl ester group is carried out with base, preferably aqueous methanolic solution of potassium hydroxide at room temperature, than the acid is liberated with 10% aqueous potassium dihydrogenphosphate solution.

After filtration of the catalyst the product is isolated by concentration of the filtrate. The product obtained on concentration is 98-99% pure, the yield is 50-70%.

The advantages of this procedure are as follows:

— the obtained product is very pure

— the number of reaction steps is less than in the known procedures

— the lactam compound, which is very difficult to remove, is not formed

— neither special pressure resistant equipment nor expensive catalyst is needed

— the final product can be obtained without applying difficult and complicated ion-exchange technology

— no poisonous or dangerous materials are needed

Examples

Example 1

a) Synthesis of 1-(nitromethyl)cyclohexyl-acetic acid

A solution of 4.3 g (0.02 mol) of methyl 1-(nitromethyl)cyclohexyl-acetate in a mixture of 50 ml of methanol and 20 ml of 10% aqueous potassium hydroxide is stirred at room temperature for 24 h, then the methanol is distilled off in vacuo. The pH of the resulted aqueous solution is adjusted to 7 with 10% aqueous potassium dihydrogenphosphate solution. The

solution is extracted three times with 30 ml of ethyl acetate, the combined organic layers are dried over sodium sulphate and concentrated to yield 3.2 g (80%) of the title compound as oil.

b) Synthesis of 1-(aminomethyl)cyclohexyl-acetic acid

A solution of 2.01 g (0.01 mol) of 1-(nitromethyl)cyclohexyl-acetic acid in 50 ml of methanol is hydrogenated in the presence of 0.2 g of palladium on activated carbon at atmospheric pressure. The catalyst is filtered off and the filtrate is concentrated to 10 ml. 20 ml of tetrahydrofuran is added to the residue and the precipitated crystals were filtered off and dried to yield 1.3 g (80%) of the title compound. Mp:164-169°C

Example 2

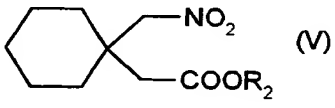
Synthesis of 1-(aminomethyl)cyclohexyl-acetic acid

A solution of 5 g (0.017 mol) of benzyl 1-(nitromethyl)cyclohexyl-acetate in 50 ml of methanol is added to a mixture of 0.5 g of prehydrogenated palladium, 10% on activated carbon in 50 ml of methanol. This mixture is hydrogenated at room temperature under atmospheric pressure until the calculated hydrogen is consumed, then the catalyst is filtered off, the filtrate is concentrated to about 15 ml and 30 ml of tetrahydrofuran is added to precipitate the title compound. Yield: 1.5 g (51%). Mp: 168°C.

Claims:

1. Process for the synthesis of 1-(aminomethyl)cyclohexyl-acetic acid and pharmaceutically acceptable salt thereof characterised by

a) transformation of the alkyl ester of cyclohexylidene-acetic acid of formula (VI) — wherein R_2 represents C_1-C_4 alkyl group — into the alkyl ester of 1-(nitromethyl)cyclohexyl-acetic acid of formula (V) — wherein the meaning of R_2 is as defined above — with nitromethane in the presence of a base, hydrolysis with aqueous methanolic solution of potassium hydroxide and hydrogenation of the obtained 1-(nitromethyl)cyclohexyl-acetic acid of formula (IIa) in the presence of a catalyst and in given case transformation of the obtained compound into a pharmaceutically acceptable salt or



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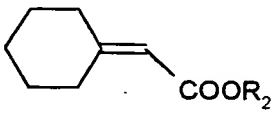

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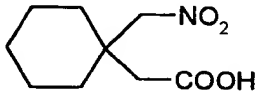
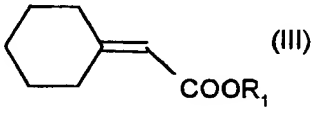


(IIa)

b) hydrolysis of the alkyl ester of cyclohexylidene-acetic acid of formula (VI) — wherein R_2 represents C_1-C_4 alkyl group — into the cyclohexylidene-acetic acid of formula (IV) with aqueous methanolic solution of potassium hydroxide, reaction of the obtained acid of formula (IV) with a reagent of formula R_1-X — wherein R_1 represents benzyl group, diphenylmethyl group or in given case C_1-C_4 alkyl or alkoxy aromatic ring substituted derivatives thereof and X represents halogen atom — to give the intermedier cyclohexylidene acid derivative of formula (III) — wherein the meaning of R_1 is as defined above — transformation of this intermedier into the 1-(nitromethyl)cyclohexyl-acetic acid derivative of formula (IIb) — wherein the meaning of R_1 is as defined above — and

hydrogenation of the latter in a solvent in the presence of a catalyst and in given case transformation of the obtained compound into a pharmaceutically acceptable salt.



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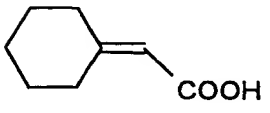

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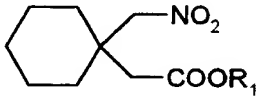

(IIb)

2. Process b) of claim 1 characterised by using benzyl halide as reagent of formula R_1-X.

3. Process b) of claim 1 characterised by using diphenylmethyl halide as reagent of formula R_1-X.

4. The process of claim 1-3 characterised by carrying out the hydrogenation in an inert organic solvent.

5. The process of claim 1-3 characterised by using palladium on activated carbon as catalyst.

6. The new compounds of formula (II), wherein R represents hydrogen, benzyl, diphenylmethyl group or in given case C_1-C_4 alkyl or alkoxy aromatic ring substituted derivatives thereof.

7. 1-(nitromethyl)cyclohexyl-acetic acid

8. benzyl 1-(nitromethyl)cyclohexyl-acetate

9. diphenylmethyl 1-(nitromethyl)cyclohexyl-acetate

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 99/00102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C227/04 C07C229/28 C07C205/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	BRYANS J S ET AL: "Investigation into the preferred conformation of Gabapentin for interaction with its binding site on the alpha2delta subunit of a calcium channel" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 7, no. 19, 7 October 1997 (1997-10-07), pages 2481-2484, XP004136469 ISSN: 0960-894X the whole document --- -/--	1,4,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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INTERNAT AL SEARCH REPORT

Inte[redacted]al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 414 263 A (GOEDECKE AG) 27 February 1991 (1991-02-27) abstract	1
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A	GARETH GRIFFITHS ET AL: "Novel Syntheses of Gabapentin via Addition of Hydrocyanic Acid to Cyclohexylidenemalonate or Cyano(cyclohexylidene)acetate" HELVETICA CHIMICA ACTA,CH,VERLAG HELVETICA CHIMICA ACTA. BASEL, vol. 74, no. 2, 1991, pages 309-314, XP002100736 ISSN: 0018-019X the whole document	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[redacted]nal Application No
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